



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



Publication number: **0 247 892 B1**

⑫

## EUROPEAN PATENT SPECIFICATION

⑬ Date of publication of patent specification: 24.04.91 ⑮ Int. Cl.<sup>5</sup>: C07D 253/06, A61K 31/53

⑰ Application number: 87304776.5

⑱ Date of filing: 29.05.87

The file contains technical information submitted  
after the application was filed and not included in  
this specification

404-815-3593

⑤<sup>a</sup> Triazine salt.

⑳ Priority: 30.05.86 GB 8613183

㉑ Date of publication of application:  
02.12.87 Bulletin 87/49

㉒ Publication of the grant of the patent:  
24.04.91 Bulletin 91/17

㉓ Designated Contracting States:  
AT BE CH DE ES FR GB GR IT LI LU NL SE

㉔ References cited:  
EP-A- 0 021 121  
EP-A- 0 024 351  
EP-A- 0 093 186  
EP-A- 0 142 306

CHEMICAL ABSTRACTS, vol. 94, no. 20, May  
18, 1981, Columbus, Ohio, USA YALCINDAG,  
O.N. "microchemical identification of drugs  
with an amidine group. IV. Hexamidine  
dilssethionate.", page 394, column 2, abstract  
no. 162824q

JOURNAL OF PHARMACEUTICAL SCIENCES,  
Jan. 1977, vol.66, no. 1, pages 1-19

㉕ Proprietor: THE WELLCOME FOUNDATION  
LIMITED  
Unicorn House 160 Euston Road  
London NW1 2BP(GB)

㉖ Inventor: Sawyer, David Alan  
The Wellcome Research Laboratories  
Langley Court Beckenham Kent(GB)  
Inventor: Copp, Frederick Charles  
32, Stanley Avenue  
Beckenham Kent(GB)

㉗ Representative: Stott, Michael John et al  
The Wellcome Research Laboratories Group  
Patents & Agreements Langley Court  
Beckenham Kent BR3 3BS(GB)

EP 0 247 892 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

## Description

This invention relates to a highly soluble triazine salt.

It is known that certain 3,5-Diamino-6-(substituted phenyl)-1,2,4-triazines are active in the treatment of CNS disorders, such as psychiatric and neurological disorders, and are also useful as anticonvulsants, for example in the treatment of epilepsy. These triazines are also non-depressant at therapeutic dose levels and are therefore advantageous as compared with depressant anti-epileptics such as phenobarbitone.

A particularly preferred compound of this type is 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (e.g. European Patent 21121). For parenteral administration the compound is desirably presented in the form of a sterile aqueous solution suitable for injection. However, the compound is only sparingly soluble in water necessitating administration of an undesirably large volume of solution to achieve a therapeutic dosage. Common pharmaceutically acceptable salts of the compound e.g. the citrate, tartrate, maleate, sterate, succinate, fumarate, phosphate, sulphate, benzenesulphonate, 4-toluenesulphonate, 4-acetoamidobenzoate and N-acetylglycinate, all have solubilities below 20mg/ml. However, we have surprisingly found that the 2-hydroxyethanesulphonate, hereinafter referred to as the isethionate, has a much higher water solubility.

Thus the present invention provides 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.

The present invention provides in particular crystalline 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.

The isethionate salt of this compound may be prepared by reacting the compound or its salt with isethionic acid and its salt.

Thus the present invention also provides a process for producing 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate which process comprises reacting 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine with isethionic acid.

Preferably the molar ratio of triazine to acid is from 1:3 to 3:1, and in particular approximately 1:1.

Isethionic acid decomposes and is therefore conveniently made *in situ* when carrying out the process of the invention. For example an alkali metal isethionate in solution is converted to isethionic acid e.g. by passing an aqueous solution of the isethionate through an H<sup>+</sup>-ion-exchange resin, and the triazine is then mixed with the resulting acid solution. Typically the reaction solvent is water and when this is so the reaction may be performed at temperatures of from 4 to 50 °C, conveniently at ambient temperature and without the need for any pH adjusters or other additives.

The isethionate salt formed may be recrystallized from e.g. Industrial Methylated Spirit to produce crystals of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate which readily dissolve in water.

The present invention further provides a process for producing 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4 triazine isethionate which process comprises reacting a 3,5 Diamino-6-(2,3-dichlorophenyl)-1,2,4 triazine salt other than isethionate with an isethionate anion. Preferably the ratio of salt to anion is from 1:50 to 50:1. More preferably the ratio is approximately 1:10. Preferably the reaction is carried out by eluting a solution of the salt in methanol through a column of isethionate anion exchange resin.

In this case the 3,5-Diamino-6-(2,3 dichlorophenyl)-1,2,4 triazine salt is preferably 3,5 Diamino-6-(2,3 dichlorophenyl)-1,2,4 triazine mesylate.

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine may be made as the base by the process described in European Patent No. 21121 by cyclization 2-(2,3-dichlorophenyl)-2-(guanidinoimino) acetonitrile.

An alternative method of making the triazine base is to react aminoguanidine with benzoyl cyanide. This may be done by reacting acidified (e.g. with an inorganic acid) aminoguanidine bicarbonate with benzoyl cyanide and refluxing in a C<sub>1</sub>-C<sub>4</sub> alcohol.

The cyclization reaction is normally carried out by refluxing in an alcohol, preferably a C<sub>1-4</sub> alcohol such as methanol or ethanol, in the presence of a strong base such as potassium hydroxide. The preparation of the starting compound for the cyclization reaction is analogous to that described in the literature i.e. U.S. Patent No. 3637688 for structurally related compounds.

We have now found that the cyclisation reaction can be carried out in the presence of a strong acid.

The present invention also provides a pharmaceutical formulation comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate, and a pharmaceutically acceptable diluent or carrier.

Although the isethionate salt is advantageously administered as a sterile aqueous formulation, either orally or parenterally, it may also be prepared as a suppository, or applied topically as an ointment, cream or powder.

For oral administration the salt may be presented in a draught, in water or in a syrup, in capsules or sachets in the dry state or in non-aqueous suspension in which suspending agents may be included. Alternatively, the salt may be presented as an effective unit dosage, for instance, compressed as a tablet or the like. The usual

pharmaceutically acceptable additives may also be present e.g. flavouring, colouring, preserving, suspending, thickening or emulsifying agents.

The present invention also provides sterile aqueous pharmaceutical formulations comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.

The salt will be present in the aqueous formulation of the present invention in an amount sufficient to be effective against CNS disorders *in vivo* and the formulation may be in unit dosage form. Up to about 250mg/ml of the salt, calculated as free base, may be present in aqueous formulation. However, typical concentrations of the salt in solution are 10 to 70mg/ml, preferably 10 to 50mg/ml. For parenteral administration the salt may be presented in sterile aqueous injection solutions which may contain therapeutically acceptable accessory ingredients such as anti-oxidants, buffers and agents to adjust the osmolarity of the solution. Preferably anions such as chloride and phosphates are not present in the solution, since these tend to exchange with the isethionate salt to form precipitates.

The present invention also provides a process for producing an aqueous formulation comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate which process comprises dissolving the isethionate in aqueous media, suitably sterile water for injection. The solution may be diluted before use to the required concentration. It is not generally necessary to adjust the pH of the solution.

The present invention can also be used to treat a human or animal suffering from or susceptible to a CNS disorder by administering to the human or animal an effective dose of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.

The present invention can also be used to treat a human or animal suffering or susceptible to a CNS disorder by administering to the human or animal an effective amount of a pharmaceutical formulation comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate and a pharmaceutically acceptable diluent or carrier.

The present invention can further also be used to treat a human or animal suffering from or susceptible to a CNS disorder by administering to the human or animal an effective amount of a sterile aqueous formulation comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate. Preferably treatment is by parenteral administration.

If the aqueous formulation is to be administered parenterally then, preferably, it is a simple aqueous solution which is diluted with, and infused in, a dextrose solution e.g. a 5% dextrose solution, at the time of administration. If dextrose is present in the aqueous formulation for long periods of time at elevated temperature e.g. during long-term stor-

age, there is a tendency for the monoglucoside of the isethionate salt to form, and it is therefore preferred to add the dextrose at the time of administration.

The present invention also provides 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

The present invention also provides a pharmaceutical formulation comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate and a pharmaceutically acceptable diluent or carrier for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

The present invention further provides an aqueous formulation comprising 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

The salt, and pharmaceutical and aqueous formulations of the present invention may be used for the treatment of CNS disorders, and in particular epilepsy, in humans.

The dose is normally for 0.1mg/kg to 30mg/kg per day of the salt, calculated as free base, preferably 0.3mg/kg to 6mg/kg per day. The dosage for adult humans is generally from 8mg to 2400mg per day of the salt, calculated as the free base, and preferably 25 to 400mg per day and this may be given as a single dose or in divided doses. Since the salt is extremely long acting, it may often be advantageous to administer an initial dose of 70 to 2400mg the first day and then a lower dose of 20 to 1200mg on subsequent days.

The following Examples illustrate the preparation of the salt of the invention and formulations containing it.

#### Example 1

Preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

A solution of 2,3-dichlorophenyl cyanide (32g, 0.16M) in dimethylsulphoxide (80mls) was added dropwise to a stirred suspension of aminoguanidine bicarbonate (81.67g, 0.6M) which had been treated with 8N aqueous nitric acid (400mls) at a temperature of about 25°C. The mixture was stirred for three hours, then left to stand at room temperature for seven days. The cooled mixture was stirred and basified with 0.880 aqueous ammonia (400mls) at 20°C, then stirred with ice cooling for thirty min-

utes, filtered and the resulting solid washed thoroughly with water and finally dried in vacuo. The above solid was added to a 10% solution of potassium hydroxide pellets in methanol (400mls) and the solution heated to reflux for one and a half hours. When cool the solution was evaporated down in vacuo, treated with ice water (800mls) then stirred for thirty minutes and filtered. The residue was dried and recrystallised for isopropanol to give 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Yield 6.8g (15.6%), m.p. 216-218 °C.

#### Example 2

Preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

Aminoguanidine bicarbonate (48.1g, 0.354M), followed by a solution of 2,3-dichlorophenyl cyanide (40.0g, 0.2M) in acetonitrile (160mls), was added to a stirred solution of concentrate sulphuric acid (441g) in water (240mls). The mixture was stirred at 20-30 °C for forty-eight hours and then filtered. The solid was added to a cooled solution of sodium hydroxide (28g) in water (150mls) below 30 °C. The suspension was filtered and the resulting solid washed thoroughly with water and dried at 80 °C. The above solid was added to propan-1-ol (308mls) and the solution heated to reflux for one and a half hours. When cool the solid was filtered, dried at 100 °C and then recrystallised from propan-1-ol to give 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Yield 21.0g (41%), m.p. 216-218 °C.

#### Example 3

Preparation of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.

A solution of sodium isethionate (148g, 1.0M) in water (4.9 litres) was passed down a column of IR 120 (H) ion-exchange resin and eluted with water. 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (256g, 1.0M) was dissolved in the resulting isethionic acid, and the solution filtered and evaporated in vacuo. The residue was recrystallised from Industrial Methylated Spirit to afford 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate. Yield 273.3g (72%), m.p. 242 °C.

#### Example 4

Preparation of 3,5 Diamino-6-(2,3,dichlorophenyl)-1,2,4-triazine isethionate.

50 mM of Amberlite (trade mark) IR-45 (OH) was mixed with 15 mM (10ml) aqueous isethionic acid and the resulting material was packed into a column. The column was then washed with methanol. 0.7g (2mM) of a methanolic solution of 3,5 Diamino-6-(2,3 dichlorophenyl)-1,2,4 triazine mesylate was eluted through the column. The elutant was recrystallised from Industrial Methylated Spirits and gave 3,5 Diamino-6-(2,3-dichlorophenyl)-1,2,4 triazine isethionate: yield 300mg (40%), m.p. 242-243 °C.

#### Example 5

74.625g (0.195M) of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate was added to and dissolved in around 900ml of water for injections BP, and diluted to 1000ml with further water for injections BP, to give an aqueous solution containing isethionate salt equivalent to 50mg/ml of the 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine base. This solution was acceptable on tonicity grounds.

#### Example 6

14.925 (0.039M) of 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate was added to a solution of 43.8g (0.221M) of Dextrose Monohydrate in around 900ml of water for injections BP and diluted to 1000ml with further water for injections BP, to give an aqueous solution containing isethionate salt equivalent to 10mg/ml of the 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine base. This solution was acceptable on tonicity grounds.

#### Claims

1. 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.
2. Crystalline 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate.
3. A compound as claimed in claim 1 or 2 for use in medicine.
4. A compound as claimed in claim 1 or 2 for use in the treatment of epilepsy.
5. An aqueous pharmaceutical formulation com-

prising a compound as claimed in claim 1 or 2.

6. A pharmaceutical formulation comprising a compound as claimed in claim 1 or 2, in admixture with a pharmaceutically acceptable diluent or carrier.
7. A formulation as claimed in claim 6 wherein the diluent is a dextrose solution.
8. A formulation as claimed in any one of claims 5 to 7 for use in medicine.
9. A formulation as claimed in any one of claims 5 to 7 for use in the treatment of epilepsy.
10. A process for the production of a compound as claimed in claim 1 or 2 comprising reacting 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine with isethionic acid.
11. A process for the production of a compound as claimed in claim 1 or 2 comprising reacting a 3,5 diamino-6-(2,3 dichlorophenyl)-1,2,4 triazine salt other than isethionate with an isethionate anion.

Claims for the following Contracting States: AT, ES, GR

1. A process for producing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate comprising reacting 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine with isethionic acid.
2. A process as claimed in claim 1 wherein the molar ratio of triazine to acid is from 1:3 to 3:1.
3. A process as claimed in claims 1 or 2 wherein the molar ratio of triazine to acid is approximately 1:1.
4. A process for producing 3,5 diamino-6-(2,3 dichlorophenyl)-1,2,4 triazine isethionate comprising reacting a 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4 triazine salt with an isethionate anion.
5. A process as claimed in claim 4 wherein the reaction is carried out by eluting a solution of the salt in methanol through a column of isethionate anion exchange resin.
6. A process as claimed in claim 4 or 5 wherein the salt is 3,5 diamino-6-(2,3 dichlorophenyl)-1,2,4 triazine mesylate.
7. A process for producing an aqueous phar-

maceutical formulation comprising 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate which process comprises dissolving the isethionate in aqueous media.

#### Revendications

1. L'iséthionate de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine.
2. L'iséthionate de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine cristallin.
3. Composé suivant la revendication 1 ou 2, à utiliser en médecine.
4. Composé suivant la revendication 1 ou 2, à utiliser pour le traitement de l'épilepsie.
5. Composition pharmaceutique aqueuse comprenant un composé suivant la revendication 1 ou 2.
6. Composition pharmaceutique comprenant un composé suivant la revendication 1 ou 2 en mélange avec un diluant ou excipient pharmaceutiquement acceptable.
7. Composition suivant la revendication 6, dans laquelle le diluant est une solution de dextrose.
8. Composition suivant l'une quelconque des revendications 5 à 7, à utiliser en médecine.
9. Composition suivant l'une quelconque des revendications 5 à 7, à utiliser pour le traitement de l'épilepsie.
10. Procédé de production d'un composé suivant la revendication 1 ou 2, qui comprend la réaction de la 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine avec l'acide iséthionique.
11. Procédé de production d'un composé suivant la revendication 1 ou 2, qui comprend la réaction d'un sel de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine autre que l'iséthionate avec un anion iséthionate.

Revendications pour les Etats contractants suivants: AT, ES, GR

1. Procédé de production de l'iséthionate de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine, qui comprend la réaction de la 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine avec l'acide iséthionique.

2. Procédé suivant la revendication 1, dans lequel le rapport molaire de la triazine à l'acide est de 1:3 à 3:1.
3. Procédé suivant la revendication 1 ou 2, dans lequel le rapport molaire de la triazine à l'acide est à peu près de 1:1.
4. Procédé de production de l'iséthionate de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine, qui comprend la réaction d'un sel de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine avec un anion iséthionate.
5. Procédé suivant la revendication 4, dans lequel la réaction est exécutée par élution d'une solution du sel dans du méthanol dans une colonne d'une résine échangeuse d'anions iséthionate.
6. Procédé suivant la revendication 4 ou 5, dans lequel le sel est le mésylate de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine.
7. Procédé de préparation d'une composition pharmaceutique aqueuse comprenant de l'iséthionate de 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine, lequel procédé comprend la dissolution de l'iséthionate dans un milieu aqueux.

#### Ansprüche

1. 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinisäthionat.
2. Kristallines 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinisäthionat.
3. Verbindung nach Anspruch 1 oder 2 zur Verwendung in der Medizin.
4. Verbindung nach Anspruch 1 oder 2 zur Verwendung bei der Behandlung von Epilepsie.
5. Wässrige pharmazeutische Formulierung umfassend eine Verbindung nach Anspruch 1 oder 2.
6. Pharmazeutische Formulierung umfassend eine Verbindung nach Anspruch 1 oder 2 in Mischung mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
7. Formulierung nach Anspruch 6, in der das Verdünnungsmittel eine Dextroselösung ist.
8. Formulierung nach einem der Ansprüche 5 bis

7 zur Verwendung in der Medizin.

9. Formulierung nach einem der Ansprüche 5 bis 7 zur Verwendung bei der Behandlung von Epilepsie.
10. Verfahren zum Herstellen einer Verbindung nach Anspruch 1 oder 2, das das Umsetzen von 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazin mit Isäthlonsäure umfaßt.
11. Verfahren zum Herstellen einer Verbindung nach Anspruch 1 oder 2, das das Umsetzen eines anderen 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinsalzes als Isäthlonat mit einem Isäthlionatanion umfaßt.

Patentansprüche für folgende Vertragsstaaten: AT, ES, GR:

1. Verfahren zum Herstellen von 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinisäthlonat, das das Umsetzen von 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazin mit Isäthlonsäure umfaßt.
2. Verfahren nach Anspruch 1, in dem das Molverhältnis von Triazin zur Säure 1 : 3 bis 3 : 1 beträgt.
3. Verfahren nach Anspruch 1 oder 2, in dem das Molverhältnis von Triazin zur Säure ungefähr 1 : 1 beträgt.
4. Verfahren zum Herstellen von 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinisäthionat, das das Umsetzen eines 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinsalzes mit einem Isäthlonsäureanion umfaßt.
5. Verfahren nach Anspruch 4, in dem die Reaktion durch Eluieren einer Lösung des Salzes in Methanol durch eine Isäthlionatanionenaustauscherharzsäule durchgeführt wird.
6. Verfahren nach Anspruch 4 oder 5, in dem das Salz 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinmesylat ist.
7. Verfahren zum Herstellen einer 3,5-Diamino-6-(2,3-dichlorophényl)-1,2,4-triazinisäthionat umfassenden wässrigen pharmazeutischen Formulierung, welches Verfahren das Lösen des Isäthlionats in wässrigen Medien umfaßt.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**